

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## **1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 40 mg hard gastro-resistant capsules.

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 40 mg of duloxetine (as hydrochloride).

Excipients: sucrose 11.5 mg .

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Hard gastro-resistant capsule.

Opaque orange body, imprinted with '40mg' and an opaque blue cap, imprinted with '9545'.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

ARICLAIM is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI), (see section 5.1).

Treatment of diabetic peripheral neuropathic pain in adults.

### **4.2 Posology and method of administration**

#### *Stress Urinary Incontinence:*

The recommended dose of ARICLAIM is 40 mg twice daily without regard to meals. After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.

However, limited data are available to support the efficacy of ARICLAIM 20 mg twice daily.

A 20 mg capsule is also available.

The efficacy of ARICLAIM has not been evaluated for longer than 3 months in placebo-controlled studies. The benefit of treatment should be re-assessed at regular intervals.

Combining ARICLAIM with a pelvic floor muscle training (PFMT) program may be more effective than either treatment alone. It is recommended that consideration be given to concomitant PFMT.

#### *Diabetic Peripheral Neuropathic Pain:*

The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

The medicinal product response should be evaluated after 2 months' of treatment. Additional response after this time is unlikely (see 5.1).

The therapeutic benefit should regularly (at least every three months) be reassessed.

*Hepatic insufficiency:*

ARICLAIM should not be used in patients with liver disease resulting in hepatic impairment (see section 4.3).

*Renal insufficiency:*

No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). ARICLAIM should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

*Elderly*

No dosage adjustment is recommended for elderly patients solely on the basis of age. Caution should be exercised when treating the elderly

*Children and adolescents:*

There is no experience in children (see section 4.4).

*Discontinuation of treatment:*

Abrupt discontinuation should be avoided. When stopping treatment with ARICLAIM the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Liver disease resulting in hepatic impairment (see section 5.2).

ARICLAIM should not be used in combination with nonselective, irreversible Monoamine Oxidase Inhibitors - MAOIs (see section 4.5).

ARICLAIM should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacin since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with ARICLAIM is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

### **4.4 Special warnings and precautions for use**

*Mania and Seizures*

ARICLAIM should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

*Use with antidepressants*

The use of ARICLAIM in combination with antidepressants (especially with SSRI, SNRI and reversible MAOIs) is not recommended (see below “Depression, suicidal ideation and behaviour” and Section 4.5).

#### *St John's wort*

Undesirable effects may be more common during concomitant use of ARICLAIM and herbal preparations containing St John's wort (*Hypericum perforatum*).

#### *Mydriasis*

Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine in patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

#### *Blood pressure and heart rate*

Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

#### *Renal impairment*

Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

#### *Haemorrhage*

There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

#### *Discontinuation of treatment*

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a clinical trial adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with ARICLAIM and 24% of patients taking placebo.

The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally the symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

#### *Hyponatremia*

Hyponatremia has been reported rarely, predominantly in the elderly, when administering ARICLAIM. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

### *Depression, suicidal ideation and behaviour*

Although ARICLAIM is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8). Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on ARICLAIM therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of ARICLAIM is recommended (see Section 4.2).

### *Use in children and adolescents under 18 years of age*

No clinical trials have been conducted with duloxetine in paediatric populations. ARICLAIM should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

### *Medicinal products containing duloxetine*

Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive episodes as well as stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

### *Hepatitis/increased liver enzymes*

Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

### *Akathisia/psychomotor restlessness*

The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

### *Sucrose*

ARICLAIM gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

*Monoamine oxidase inhibitors (MAOIs):* due to the risk of serotonin syndrome, ARICLAIM should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping ARICLAIM before starting an MAOI (see section 4.3).

*Serotonin syndrome:* in rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if ARICLAIM is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (*Hypericum perforatum*), venlafaxine or triptans, tramadol, pethidine and tryptophan.

*CNS medicinal products:* caution is advised when ARICLAIM is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

### *Effect of duloxetine on other medicinal products*

*Medicinal products metabolised by CYP1A2:* The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).

*Medicinal products metabolised by CYP2D6:* Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if ARICLAIM is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

*Oral contraceptives and other steroidal agents:* results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

*Anticoagulants and antiplatelet agents:* Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin.

### *Effects of other medicinal products on duloxetine*

*Antacids and H<sub>2</sub> antagonists:* co-administration of ARICLAIM with aluminium- and magnesium-containing antacids or with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

*Inhibitors of CYP1A2:* because CYP1A2 is involved in duloxetine metabolism, concomitant use of ARICLAIM with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC<sub>0-1</sub> 6-fold. Therefore ARICLAIM should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

*Inducers of CYP1A2:* Population pharmacokinetic studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

## 4.6 Pregnancy and lactation

### *Pregnancy*

There are no data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3). The potential risk for humans is unknown. As with other serotonergic medicinal product, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. ARICLAIM should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

### *Breast feeding*

Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of ARICLAIM while breast-feeding is not recommended.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. ARICLAIM may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

## 4.8 Undesirable effects

### *Stress Urinary Incontinence:*

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7976 patients, 4370 on duloxetine and 3606 on placebo) in SUI and other lower urinary tract disorders.

The most commonly reported adverse events in patients treated with ARICLAIM in clinical trials in SUI and other lower urinary tract disorders were nausea, dry mouth fatigue and constipation. The data analysis of four 12-week, placebo-controlled clinical trials in patients with SUI, including 958 duloxetine-treated and 955 placebo-treated patients, showed that the onset of the reported adverse events typically occurred in the first week of therapy. However, the majority of the most frequent adverse events were mild to moderate and resolved within 30 days of occurrence (e.g. nausea).

### *Table 1: Adverse reactions*

Frequency estimate: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1,000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
<i>Investigations</i>					
		Weight decrease Weight increase Blood cholesterol increased	Creatinine phosphokinase increase		
<i>Cardiac Disorders</i>					
	Palpitations	Tachycardia			Supra-ventricular arrhythmia, mainly atrial fibrillation
<i>Nervous System Disorders</i>					
	Headache Dizziness Tremor Lethargy Somnolence Paraesthesia	Poor quality of sleep Disturbance in attention Nervousness Dysgeusia	Dyskinesia Myoclonus		Serotonin syndrome Psychomotor restlessness Convulsions Akathisia Extrapyramidal symptoms
<i>Eye Disorders</i>					
	Blurred vision	Visual disturbance Mydriasis	Glaucoma		
<i>Ear and Labyrinth Disorders</i>					
	Vertigo	Tinnitus <sup>1</sup> Ear pain			
<i>Respiratory, thoracic and mediastinal disorders</i>					
		Yawning	Epistaxis Throat tightness		
<i>Gastrointestinal Disorders</i>					
Nausea (23.3%) Dry mouth (11.9%) Constipation (10.3%)	Diarrhoea Vomiting Dyspepsia	Gastroenteritis Stomatitis Gastritis Flatulence Eructation Breath odour	Haematochezia		Gastrointestinal haemorrhage
<i>Renals and Urinary Disorders</i>					
		Urinary hesitation Dysuria Nocturia Urine odour abnormal	Urine flow decreased Polyuria		Urinary retention
<i>Skin and Subcutaneous Tissue Disorders</i>					
	Sweating increased	Rash Increased tendency to	Photo-sensitivity reactions		Stevens-Johnson Syndrome Angioneurotic oedema



Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		bruise Night sweats Cold sweat	Dermatitis contact Urticaria		
<i>Muscoskeletal and connective tissue disorders</i>					
		Muscle spasm Muscle tightness Musculo-skeletal pain Trismus	Muscle twitching		
<i>Endocrine disorders</i>					
		Hypo-thyroidism			
<i>Metabolism and Nutrition Disorders</i>					
	Appetite decreased	Dehydration	Hyperglycemia (reported especially in diabetic patients) SIADH Hyponatremia		
<i>Infections and infestations</i>					
		Laryngitis			
<i>Vascular Disorders</i>					
	Flushing	Syncope <sup>2</sup> Blood pressure increase	Hypertensive crisis Orthostatic hypotension <sup>2</sup> Peripheral coldness		Hypertension
<i>General Disorders and Administration Site Conditions</i>					
Fatigue (10.9%)	Abdominal pain Pruritus Weakness Chills	Malaise Feeling hot Feeling abnormal Thirst	Gait disturbance Feeling cold		Chest pain
<i>Immune system disorders</i>					
		Hyper-sensitivity disorder	Anaphylactic reaction		
<i>Hepato-biliary disorders</i>					
		Hepatitis <sup>3</sup> Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury			Hepatic failure Jaundice
<i>Reproductive System and Breast Disorders</i>					
		Menopausal			

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		symptoms Gynaecological haemorrhage			
<i>Psychiatric Disorders</i>					
	Insomnia Anxiety Sleep disorder Agitation Libido decreased	Disorientation Abnormal dreams Apathy Bruxism Orgasm abnormal	Hallucinations		Suicidal behaviour Suicidal ideation <sup>4</sup> Mania Aggression and anger <sup>5</sup>

<sup>1</sup>Cases of tinnitus have also been reported after treatment discontinuation.

<sup>2</sup>Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment

<sup>3</sup>See section 4.4

<sup>4</sup>Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4)

<sup>5</sup>Cases of aggression and anger have been reported particularly early in treatment of after treatment discontinuation.

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhidrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Electrocardiograms were obtained from 755 duloxetine-treated patients with SUI and 779 placebo-treated patients in 12-week clinical trials. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients.

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA<sub>1c</sub> was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA<sub>1c</sub> in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

#### *Diabetic Peripheral Neuropathic Pain*

Table 2 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 5253 patients, 3289 on duloxetine and 1964 on placebo).

The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with ARICLAIM were: nausea; headache, dry mouth and somnolence.

*Table 2: Adverse reactions*

Frequency estimate: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1,000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
<i>Investigations</i>					
	Weight decrease	Weight increase Creatinine phosphokinase increase	Blood cholesterol increased		
<i>Cardiac Disorders</i>					
	Palpitations	Tachycardia	Supra-ventricular arrhythmia, mainly atrial fibrillation		
<i>Nervous System Disorders</i>					
Headache (13.8%) Somnolence (10.7%)	Dizziness Tremor Lethargy Paraesthesia	Dyskinesia Poor quality sleep Nervousness Myoclonus Disturbance in attention Dysgeusia			Serotonin syndrome Convulsions Akathisia Psychomotor restlessness Extra-pyramidal symptoms
<i>Eye Disorders</i>					
	Blurred vision	Visual disturbance Mydriasis	Glaucoma		
<i>Ear and Labyrinth Disorders</i>					
	Tinnitus <sup>1</sup>	Vertigo Ear pain			
<i>Respiratory, thoracic and mediastinal disorders</i>					
	Yawning	Epistaxis Throat tightness			
<i>Gastrointestinal Disorders</i>					
Nausea (21.7%) Dry mouth (13.2%)	Diarrhoea Constipation Vomiting Dyspepsia Flatulence	Gastroenteritis Stomatitis Gastritis Eructation	Haematochezia Breath odour		Gastrointestinal haemorrhage
<i>Renals and Urinary Disorders</i>					
		Urinary Retention Urinary hesitation Dysuria Nocturia			Urine odour abnormal

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		Polyuria Urine flow decreased			
<i>Skin and Subcutaneous Tissue Disorders</i>					
	Rash Sweating increased Night sweats	Photo-sensitivity reactions Increased tendency to bruise Dermatitis contact Urticaria Cold sweat			Stevens-Johnson Syndrome Angio-neurotic oedema
<i>Musculoskeletal and connective tissue disorders</i>					
	Musculo-skeletal pain Muscle tightness Muscle spasm	Muscle twitching	Trismus		
<i>Endocrine disorders</i>					
			Hypo-thyroidism		
<i>Metabolism and Nutrition Disorders</i>					
	Decreased Appetite	Hyperglycemia (reported especially in diabetic patients)	Dehydration SIADH Hypo-natremia		
<i>Infections and infestations</i>					
		Laryngitis			
<i>Vascular Disorders</i>					
	Flushing	Syncope <sup>2</sup> Orthostatic hypotension <sup>2</sup> Blood pressure increase Peripheral coldness			Hypertensive crisis Hypertension
<i>General Disorders and Administration Site Conditions</i>					
	Fatigue Abdominal pain	Feeling hot Malaise Gait disturbance Feeling abnormal Feeling cold Thirst Chills			Chest pain
<i>Immune system disorders</i>					
		Hyper-sensitivity	Anaphylactic reaction		

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		disorder			
<i>Hepato-biliary disorders</i>					
		Hepatitis <sup>3</sup> Elevated liver enzymes (ALT, AST, alkaline phosphatase)  Acute liver injury			Hepatic failure Jaundice
<i>Reproductive System and Breast Disorders</i>					
	Erectile dysfunction	Sexual dysfunction Ejaculation disorder Ejaculation delayed Gynaecological haemorrhage	Menopausal symptoms		
<i>Psychiatric Disorders</i>					
	Insomnia Abnormal dreams Anxiety Agitation Libido decreased Orgasm abnormal	Sleep disorder Apathy Disorientation Bruxism	Aggression and anger <sup>5</sup> Mania		Suicidal behaviour <sup>4</sup> Suicidal ideation <sup>4</sup> Hallucinations

<sup>1</sup> Cases of tinnitus have also been reported after treatment discontinuation.

<sup>2</sup> Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.

<sup>3</sup> See section 4.4

<sup>4</sup> Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4)

<sup>5</sup> Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhidrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in

duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Electrocardiograms were obtained from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

#### **4.9 Overdose**

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 4800mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote for duloxetine is known but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered.. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21

Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the storage phase of the micturition cycle. A similar mechanism in women is believed to result in stronger urethral closure during urine storage with physical stress that could explain the efficacy of duloxetine in the treatment of women with SUI.

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

**Stress Urinary Incontinence:** The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies, that randomised 1913 women (22 to 83 years) with SUI; of these, 958 patients were randomised to duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).

**Incontinence Episode Frequency:** in all four studies the duloxetine-treated group had a 50% or greater median decrease in IEF compared with 33% in the placebo-treated group. Differences were observed at each visit after 4 weeks (duloxetine 54%; and placebo 22%), 8 weeks (52% and 29%), and 12 weeks (52% and 33%) of medication.

In an additional study limited to patients with severe SUI, all responses with duloxetine were achieved within 2 weeks.

The efficacy of ARICLAIM has not been evaluated for longer than 3 months in placebo-controlled studies. The clinical benefit of ARICLAIM compared with placebo has not been demonstrated in women with mild SUI, defined in randomised trials as those with IEF < 14 per week. In these women, ARICLAIM may provide no benefit beyond that afforded by more conservative behavioural interventions.

*Quality of Life:* Incontinence Quality of Life (I-QOL) questionnaire scores were significantly improved in the duloxetine-treated patient group compared with the placebo-treated group (9.2 versus 5.9 score improvement,  $p < .001$ ). Using a global improvement scale (PGI), significantly more women using duloxetine considered their symptoms of stress incontinence to be improved with treatment compared with women using placebo (64.6% versus 50.1%,  $p < .001$ ).

*ARICLAIM and Prior Continence Surgery:* there are limited data that suggest that the benefits of ARICLAIM are not diminished in women with stress urinary incontinence who have previously undergone continence surgery.

*ARICLAIM and Pelvic Floor Muscle Training (PFMT):* during a 12-week blinded, randomised, controlled study, ARICLAIM demonstrated greater reductions in IEF compared with either placebo treatment or with PFMT alone. Combined therapy (duloxetine + PFMT) showed greater improvement in both pad use and condition-specific quality of life measures than ARICLAIM alone or PFMT alone.

*Diabetic Peripheral Neuropathic Pain:*

The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

Although data from a one-year open label study offer some evidence for longer-term efficacy, no conclusive efficacy data for treatments longer than 12 weeks duration are available from placebo-controlled studies.

## 5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Duloxetine is well absorbed after oral administration with a  $C_{max}$  occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%; N=8 subjects). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%).

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy,6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

The elimination half-life of duloxetine after an oral dose ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

### Special populations:

**Gender:** pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

**Age:** pharmacokinetic differences have been identified between younger and elderly females ( $\geq 65$  years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

**Renal impairment:** end stage renal disease (ESRD) patients receiving dialysis had a 2-fold higher duloxetine  $C_{max}$  and AUC values compared to healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

**Hepatic insufficiency:** moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

**Nursing mothers:** The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7  $\mu\text{g/day}$  while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.



### **5.3 Preclinical safety data**

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown.

Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposures levels below maximum clinical exposure (AUC).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### **Capsule content:**

Hypromellose.  
Hydroxypropyl methylcellulose acetate succinate  
Sucrose  
Sugar spheres  
Talc  
Titanium dioxide (E171)  
Triethyl citrate.

#### **Capsule shell:**

Gelatin  
Sodium Lauryl Sulfate  
Titanium Dioxide (E171)  
Indigo Carmine (E132)  
Red Iron oxide (E172)  
Yellow Iron Oxide (E172)  
Edible black ink.

#### **Edible Ink:**

Black Iron Oxide-Synthetic (E172)  
Propylene glycol  
Shellac.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

3 years.

#### **6.4 Special precautions for storage**

Store in the original package in order to protect from moisture. Do not store above 30°C.

#### **6.5 Nature and contents of container**

Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminum foil.

Packs of 28, 56, 98, 140 and 196 (2x98) capsules.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

No special requirements.

### **7. MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/283/002

EU/1/04/283/003

EU/1/04/283/004

EU/1/04/283/005

EU/1/04/283/006

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

11 August 2004

### **10. DATE OF REVISION OF THE TEXT**

## **1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 20 mg hard gastro-resistant capsules.

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 20 mg of duloxetine (as hydrochloride).

Excipients: sucrose 5.7 mg.

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Hard gastro-resistant capsule.

Opaque blue body, imprinted with '20 mg' and an opaque blue cap, imprinted with '9544'.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

ARICLAIM is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI), (see section 5.1).

Treatment of diabetic peripheral neuropathic pain in adults.

### **4.2 Posology and method of administration**

#### *Stress Urinary Incontinence:*

The recommended dose of ARICLAIM is 40 mg twice daily without regard to meals. After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.

However, limited data are available to support the efficacy of ARICLAIM 20 mg twice daily.

The efficacy of ARICLAIM has not been evaluated for longer than 3 months in placebo-controlled studies. The benefit of treatment should be re-assessed at regular intervals.

Combining ARICLAIM with a pelvic floor muscle training (PFMT) program may be more effective than either treatment alone. It is recommended that consideration be given to concomitant PFMT.

#### *Diabetic Peripheral Neuropathic Pain:*

The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

The medicinal product response should be evaluated after 2 months' of treatment. Additional response after this time is unlikely (see 5.1).

The therapeutic benefit should regularly (at least every three months) be reassessed.

#### *Hepatic insufficiency:*

ARICLAIM should not be used in patients with liver disease resulting in hepatic impairment (see section 4.3).

*Renal insufficiency:*

No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). ARICLAIM should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

*Elderly:*

No dosage adjustment is recommended for elderly patients solely on the basis of age. Caution should be exercised when treating the elderly.

*Children and adolescents:*

There is no experience in children (see section 4.4).

*Discontinuation of treatment:*

Abrupt discontinuation should be avoided. When stopping treatment with ARICLAIM the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.).

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Liver disease resulting in hepatic impairment (see section 5.2).

ARICLAIM should not be used in combination with nonselective, irreversible Monoamine Oxidase Inhibitors - MAOIs (see section 4.5).

ARICLAIM should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacin since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with ARICLAIM is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

### **4.4 Special warnings and precautions for use**

*Mania and Seizures*

ARICLAIM should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

*Use with antidepressants*

The use of ARICLAIM in combination with antidepressants (especially with SSRI, SNRI and reversible MAOIs) is not recommended (see below “Depression, suicidal ideation and behaviour” and Section 4.5).

#### *St John's wort*

Undesirable effects may be more common during concomitant use of ARICLAIM and herbal preparations containing St John's wort (*Hypericum perforatum*).

#### *Mydriasis*

Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine in patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

#### *Blood pressure and heart rate*

Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

#### *Renal impairment*

Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

#### *Haemorrhage*

There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

#### *Discontinuation of treatment*

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a clinical trial, adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with ARICLAIM and 24% of patients taking placebo.

The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally the symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

#### *Hyponatremia*

Hyponatremia has been reported rarely, predominantly in the elderly, when administering ARICLAIM. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

### *Depression, suicidal ideation and behaviour*

Although ARICLAIM is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8). Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on ARICLAIM therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of ARICLAIM is recommended (see Section 4.2).

### *Use in children and adolescents under 18 years of age*

No clinical trials have been conducted with duloxetine in paediatric populations. ARICLAIM should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. Long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

### *Medicinal products containing duloxetine*

Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive episodes as well as stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

### *Hepatitis/increased liver enzymes*

Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

### *Akathisia/psychomotor restlessness*

The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

### *Sucrose*

ARICLAIM gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

## 4.5 Interaction with other medicinal products and other forms of interaction

*Monoamine oxidase inhibitors (MAOIs):* due to the risk of serotonin syndrome, ARICLAIM should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping ARICLAIM before starting an MAOI (see section 4.3).

*Serotonin syndrome:* in rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if ARICLAIM is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (*Hypericum perforatum*), venlafaxine or triptans, tramadol, pethidine and tryptophan.

*CNS medicinal products:* caution is advised when ARICLAIM is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

### *Effect of duloxetine on other medicinal products*

*Medicinal products metabolised by CYP1A2:* The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).

*Medicinal products metabolised by CYP2D6:* Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if ARICLAIM is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

*Oral contraceptives and other steroidal agents:* results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

*Anticoagulants and antiplatelet agents:* Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin.

### *Effects of other medicinal products on duloxetine*

*Antacids and H<sub>2</sub> antagonists:* co-administration of ARICLAIM with aluminium- and magnesium-containing antacids or with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

*Inhibitors of CYP1A2:* because CYP1A2 is involved in duloxetine metabolism, concomitant use of ARICLAIM with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC<sub>0-t</sub> 6-fold. Therefore ARICLAIM should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

*Inducers of CYP1A2:* Population pharmacokinetic studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

## 4.6 Pregnancy and lactation

### *Pregnancy*

There are no data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3). The potential risk for humans is unknown.

As with other serotonergic medicinal product, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. ARICLAİM should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

### *Breast feeding*

Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of ARICLAİM while breast-feeding is not recommended.

## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. ARICLAİM may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

## 4.8 Undesirable effects

### *Stress Urinary Incontinence:*

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 7976 patients, 4370 on duloxetine and 3606 on placebo) in SUI and other lower urinary tract disorders.

The most commonly reported adverse events in patients treated with ARICLAİM in clinical trials in SUI and other lower urinary tract disorders were nausea, dry mouth fatigue and constipation. The data analysis of four 12-week, placebo-controlled clinical trials in patients with SUI, including 958 duloxetine-treated and 955 placebo-treated patients, showed that the onset of the reported adverse events typically occurred in the first week of therapy. However, the majority of the most frequent adverse events were mild to moderate and resolved within 30 days of occurrence (e.g. nausea).

### *Table 1: Adverse reactions*

Frequency estimate: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1,000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.



Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
<i>Investigations</i>					
		Weight decrease Weight increase Blood cholesterol increased	Creatinine phosphokinase increase		
<i>Cardiac Disorders</i>					
	Palpitations	Tachycardia			Supra-ventricular arrhythmia, mainly atrial fibrillation
<i>Nervous System Disorders</i>					
	Headache Dizziness Tremor Lethargy Somnolence Paraesthesia	Poor quality of sleep Disturbance in attention Nervousness Dysgeusia	Dyskinesia Myoclonus		Serotonin syndrome Psychomotor restlessness Convulsions Akathisia Extrapyramidal symptoms
<i>Eye Disorders</i>					
	Blurred vision	Visual disturbance Mydriasis	Glaucoma		
<i>Ear and Labyrinth Disorders</i>					
	Vertigo	Tinnitus <sup>1</sup> Ear pain			
<i>Respiratory, thoracic and mediastinal disorders</i>					
		Yawning	Epistaxis Throat tightness		
<i>Gastrointestinal Disorders</i>					
Nausea (23.3%) Dry mouth (11.9%) Constipation (10.3%)	Diarrhoea Vomiting Dyspepsia	Gastroenteritis Stomatitis Gastritis Flatulence Eructation Breath odour	Haematochezia		Gastrointestinal haemorrhage
<i>Renals and Urinary Disorders</i>					
		Urinary hesitation Dysuria Nocturia Urine odour abnormal	Urine flow decreased Polyuria		Urinary retention
<i>Skin and Subcutaneous Tissue Disorders</i>					
	Sweating increased	Rash Increased tendency to	Photo-sensitivity reactions		Stevens-Johnson Syndrome Angioneurotic oedema

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		bruise Night sweats Cold sweat	Dermatitis contact Urticaria		
<i>Muscoskeletal and connective tissue disorders</i>					
		Muscle spasm Muscle tightness Musculo-skeletal pain Trismus	Muscle twitching		
<i>Endocrine disorders</i>					
		Hypo-thyroidism			
<i>Metabolism and Nutrition Disorders</i>					
	Appetite decreased	Dehydration	Hyperglycemia (reported especially in diabetic patients) SIADH Hyponatremia		
<i>Infections and infestations</i>					
		Laryngitis			
<i>Vascular Disorders</i>					
	Flushing	Syncope <sup>2</sup> Blood pressure increase	Hypertensive crisis Orthostatic hypotension <sup>2</sup> Peripheral coldness		Hypertension
<i>General Disorders and Administration Site Conditions</i>					
Fatigue (10.9%)	Abdominal pain Pruritus Weakness Chills	Malaise Feeling hot Feeling abnormal Thirst	Gait disturbance Feeling cold		Chest pain
<i>Immune system disorders</i>					
		Hyper-sensitivity disorder	Anaphylactic reaction		
<i>Hepato-biliary disorders</i>					
		Hepatitis <sup>3</sup> Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury			Hepatic failure Jaundice
<i>Reproductive System and Breast Disorders</i>					
		Menopausal			

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		symptoms Gynaecological haemorrhage			
<i>Psychiatric Disorders</i>					
	Insomnia Anxiety Sleep disorder Agitation Libido decreased	Disorientation Abnormal dreams Apathy Bruxism Orgasm abnormal	Hallucinations		Suicidal behaviour Suicidal ideation <sup>4</sup> Mania Aggression and anger <sup>5</sup>

<sup>1</sup>Cases of tinnitus have also been reported after treatment discontinuation.

<sup>2</sup>Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment

<sup>3</sup>See section 4.4

<sup>4</sup>Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4)

<sup>5</sup>Cases of aggression and anger have been reported particularly early in treatment of after treatment discontinuation.

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhidrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

Electrocardiograms were obtained from 755 duloxetine-treated patients with SUI and 779 placebo-treated patients in 12-week clinical trials. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients.

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA<sub>1c</sub> was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA<sub>1c</sub> in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

#### *Diabetic Peripheral Neuropathic Pain*

Table 2 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 5253 patients, 3289 on duloxetine and 1964 on placebo).

The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with ARICLAIM were: nausea; headache, dry mouth and somnolence.

*Table 2: Adverse reactions*

Frequency estimate: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1,000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
<i>Investigations</i>					
	Weight decrease	Weight increase Creatinine phosphokinase increase	Blood cholesterol increased		
<i>Cardiac Disorders</i>					
	Palpitations	Tachycardia	Supra-ventricular arrhythmia, mainly atrial fibrillation		
<i>Nervous System Disorders</i>					
Headache (13.8%) Somnolence (10.7%)	Dizziness Tremor Lethargy Paraesthesia	Dyskinesia Poor quality sleep Nervousness Myoclonus Disturbance in attention Dysgeusia			Serotonin syndrome Convulsions Akathisia Psychomotor restlessness Extra-pyramidal symptoms
<i>Eye Disorders</i>					
	Blurred vision	Visual disturbance Mydriasis	Glaucoma		
<i>Ear and Labyrinth Disorders</i>					
	Tinnitus <sup>1</sup>	Vertigo Ear pain			
<i>Respiratory, thoracic and mediastinal disorders</i>					
	Yawning	Epistaxis Throat tightness			
<i>Gastrointestinal Disorders</i>					
Nausea (21.7%) Dry mouth (13.2%)	Diarrhoea Constipation Vomiting Dyspepsia Flatulence	Gastroenteritis Stomatitis Gastritis Eructation	Haematochezia Breath odour		Gastrointestinal haemorrhage
<i>Renals and Urinary Disorders</i>					
		Urinary Retention Urinary hesitation Dysuria Nocturia			Urine odour abnormal

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		Polyuria Urine flow decreased			
<i>Skin and Subcutaneous Tissue Disorders</i>					
	Rash Sweating increased Night sweats	Photo-sensitivity reactions Increased tendency to bruise Dermatitis contact Urticaria Cold sweat			Stevens-Johnson Syndrome Angio-neurotic oedema
<i>Musculoskeletal and connective tissue disorders</i>					
	Musculo-skeletal pain Muscle tightness Muscle spasm	Muscle twitching	Trismus		
<i>Endocrine disorders</i>					
			Hypo-thyroidism		
<i>Metabolism and Nutrition Disorders</i>					
	Decreased Appetite	Hyperglycemia (reported especially in diabetic patients)	Dehydration SIADH Hypo-natremia		
<i>Infections and infestations</i>					
		Laryngitis			
<i>Vascular Disorders</i>					
	Flushing	Syncope <sup>2</sup> Orthostatic hypotension <sup>2</sup> Blood pressure increase Peripheral coldness			Hypertensive crisis Hypertension
<i>General Disorders and Administration Site Conditions</i>					
	Fatigue Abdominal pain	Feeling hot Malaise Gait disturbance Feeling abnormal Feeling cold Thirst Chills			Chest pain
<i>Immune system disorders</i>					
		Hyper-sensitivity	Anaphylactic reaction		

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		disorder			
<i>Hepato-biliary disorders</i>					
		Hepatitis <sup>3</sup> Elevated liver enzymes (ALT, AST, alkaline phosphatase)  Acute liver injury			Hepatic failure Jaundice
<i>Reproductive System and Breast Disorders</i>					
	Erectile dysfunction	Sexual dysfunction Ejaculation disorder Ejaculation delayed Gynaecological haemorrhage	Menopausal symptoms		
<i>Psychiatric Disorders</i>					
	Insomnia Abnormal dreams Anxiety Agitation Libido decreased Orgasm abnormal	Sleep disorder Apathy Disorientation Bruxism	Aggression and anger <sup>5</sup> Mania		Suicidal behaviour <sup>4</sup> Suicidal ideation <sup>4</sup> Hallucinations

<sup>1</sup>Cases of tinnitus have also been reported after treatment discontinuation.

<sup>2</sup> Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.

<sup>3</sup> See section 4.4

<sup>4</sup>Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4)

<sup>5</sup>Cases of aggression and anger have been reported particularly early in treatment of after treatment discontinuation.

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhidrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in

duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Electrocardiograms were obtained from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

#### **4.9 Overdose**

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 4800mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote for duloxetine is known but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered.. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21

Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the storage phase of the micturition cycle. A similar mechanism in women is believed to result in stronger urethral closure during urine storage with physical stress that could explain the efficacy of duloxetine in the treatment of women with SUI.

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

**Stress Urinary Incontinence:**

The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies, that randomised 1913 women (22 to 83 years) with SUI; of these, 958 patients were randomised to duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).

*Incontinence Episode Frequency:* in all four studies the duloxetine-treated group had a 50% or greater median decrease in IEF compared with 33% in the placebo-treated group. Differences were observed

at each visit after 4 weeks (duloxetine 54%; and placebo 22%), 8 weeks (52% and 29%), and 12 weeks (52% and 33%) of medication.

In an additional study limited to patients with severe SUI, all responses with duloxetine were achieved within 2 weeks.

The efficacy of ARICLAIM has not been evaluated for longer than 3 months in placebo-controlled studies. The clinical benefit of ARICLAIM compared with placebo has not been demonstrated in women with mild SUI, defined in randomised trials as those with IEF < 14 per week. In these women, ARICLAIM may provide no benefit beyond that afforded by more conservative behavioural interventions.

*Quality of Life:* Incontinence Quality of Life (I-QOL) questionnaire scores were significantly improved in the duloxetine-treated patient group compared with the placebo-treated group (9.2 versus 5.9 score improvement,  $p < .001$ ). Using a global improvement scale (PGI), significantly more women using duloxetine considered their symptoms of stress incontinence to be improved with treatment compared with women using placebo (64.6% versus 50.1%,  $p < .001$ ).

*ARICLAIM and Prior Continence Surgery:* there are limited data that suggest that the benefits of ARICLAIM are not diminished in women with stress urinary incontinence who have previously undergone continence surgery.

*ARICLAIM and Pelvic Floor Muscle Training (PFMT):* during a 12-week blinded, randomised, controlled study, ARICLAIM demonstrated greater reductions in IEF compared with either placebo treatment or with PFMT alone. Combined therapy (duloxetine + PFMT) showed greater improvement in both pad use and condition-specific quality of life measures than ARICLAIM alone or PFMT alone.

*Diabetic Peripheral Neuropathic Pain:*

The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

Although data from a one-year open label study offer some evidence for longer-term efficacy, no conclusive efficacy data for treatments longer than 12 weeks duration are available from placebo-controlled studies.



## 5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Duloxetine is well absorbed after oral administration with a  $C_{max}$  occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%; N=8 subjects). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11%).

Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both CYP2D6 and CYP1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5-hydroxy,6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

The elimination half-life of duloxetine after an oral dose ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

### Special populations:

**Gender:** pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

**Age:** pharmacokinetic differences have been identified between younger and elderly females ( $\geq 65$  years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

**Renal impairment:** end stage renal disease (ESRD) patients receiving dialysis had a 2-fold higher duloxetine  $C_{max}$  and AUC values compared to healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

**Hepatic insufficiency:** moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

**Nursing mothers:** The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7  $\mu\text{g/day}$  while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

### 5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown.

Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposures levels below maximum clinical exposure (AUC).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### **Capsule content:**

Hypromellose.  
Hydroxypropyl methylcellulose acetate succinate  
Sucrose  
Sugar spheres  
Talc  
Titanium dioxide (E171)  
Triethyl citrate.

#### **Capsule shell:**

Gelatin  
Sodium Lauryl Sulfate  
Titanium Dioxide (E171)  
Indigo Carmine (E132)  
Edible Black Ink.

#### **Edible Ink:**

Black Iron Oxide-Synthetic (E172)  
Propylene glycol  
Shellac

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30°C.

#### **6.5 Nature and contents of container**

Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminum foil.

Packs of 28 and 56 capsules.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

No special requirements.

### **7. MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

### **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/283/001  
EU/1/04/283/007

### **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

11 August 2004

### **10. DATE OF REVISION OF THE TEXT**

## **1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 30 mg hard gastro-resistant capsules

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 30 mg of duloxetine (as hydrochloride)

Excipients: sucrose 8.6 mg.

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Hard gastro-resistant capsule.

Opaque white body, imprinted with '30 mg' and an opaque blue cap, imprinted with '9543'.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of diabetic peripheral neuropathic pain in adults.

### **4.2 Posology and method of administration**

For oral use.

#### *Adults*

The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

The medicinal product response should be evaluated after 2 months' of treatment. Additional response after this time is unlikely (see 5.1).

The therapeutic benefit should regularly (at least every three months) be reassessed.

#### *Elderly*

No dosage adjustment is recommended for elderly patients solely on the basis of age. However, caution should be exercised when treating the elderly (see section 5.2).

#### *Children and adolescents*

There is no experience in children (see section 4.4).

#### *Hepatic impairment*

ARICLAIM should not be used in patients with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

#### *Renal insufficiency*

No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). ARICLAIM should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3)..

#### *Discontinuation of treatment*

Abrupt discontinuation should be avoided. When stopping treatment with ARICLAIM the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Concomitant use of ARICLAIM with nonselective, irreversible Monoamine Oxidase Inhibitors (MAOIs) is contraindicated (see section 4.5).

Liver disease resulting in hepatic impairment (see section 5.2).

ARICLAIM should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e. potent CYP1A2 inhibitors) since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with ARICLAIM is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

### **4.4 Special warnings and precautions for use**

#### *Mania and seizures*

ARICLAIM should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

#### *Mydriasis*

Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing ARICLAIM to patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

#### *Blood pressure and heart rate*

Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

#### *Renal impairment*

Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

#### *Use with antidepressants*

Caution should be exercised when using ARICLAIM in combination with antidepressants. In particular the combination with selective reversible MAOIs is not recommended.

#### *St John's wort*

Undesirable effects may be more common during concomitant use of ARICLAIM and herbal preparations containing St John's wort (*Hypericum perforatum*).

#### *Depression, suicidal ideation and behaviour*

Although ARICLAIM is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8). Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on ARICLAIM therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of ARICLAIM is recommended (see section 4.2).

#### *Use in children and adolescents under 18 years of age*

No clinical trials have been conducted with duloxetine in paediatric populations. ARICLAIM should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

#### *Haemorrhage*

There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

#### *Hyponatremia*

Hyponatremia has been reported rarely, predominantly in the elderly, when administering ARICLAIM. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

#### *Discontinuation of treatment*

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with ARICLAIM and 23% of patients taking placebo.

The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly

reported reactions are listed in section 4.8. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

#### *Akathisia/psychomotor restlessness*

The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

#### *Medicinal products containing duloxetine*

Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive episodes as well as stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

#### *Hepatitis/increased liver enzymes*

Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

#### *Sucrose*

ARICLAIM gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

### **4.5 Interaction with other medicinal products and other forms of interaction**

*CNS medicinal products:* the risk of using duloxetine in combination with other CNS-active medicinal products has not been systematically evaluated, except in the cases described in this section. Consequently, caution is advised when ARICLAIM is taken in combination with other centrally acting medicinal products and substances including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

*Monoamine Oxidase Inhibitors (MAOIs):* due to the risk of serotonin syndrome, ARICLAIM should not be used in combination with nonselective irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping ARICLAIM before starting an MAOI (see section 4.3).

For selective, reversible MAOIs, like moclobemide, the risk of serotonin syndrome is lower. However, the concomitant use of ARICLAIM with selective, reversible MAOIs is not recommended (see section 4.4).

*Serotonin syndrome:* in rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if ARICLAIM is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (*Hypericum perforatum*), venlafaxine or triptans, tramadol, pethidine and tryptophan.

#### *Effect of duloxetine on other medicinal products*

*Medicinal products metabolised by CYP1A2:* The pharmacokinetics of theophylline, a CYP1A2

substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily). *Medicinal products metabolised by CYP2D6*: Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if ARICLAIM is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

*Oral contraceptives and other steroidal agents*: results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

*Anticoagulants and antiplatelet agents*: Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin.

#### *Effects of other medicinal products on duloxetine*

*Antacids and H<sub>2</sub> antagonists*: co-administration of duloxetine with aluminium- and magnesium-containing antacids or duloxetine with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

*Inhibitors of CYP 1A2*: because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC<sub>0-1</sub> 6-fold. Therefore ARICLAIM should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

*Inducers of CYP1A2*: Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

## **4.6 Pregnancy and lactation**

### *Pregnancy*

There are no data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3).

The potential risk for humans is unknown. As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. ARICLAIM should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

### *Breast feeding*

Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of ARICLAIM while breast-feeding is not recommended.



## 4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. ARICLAIM may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

## 4.8 Undesirable effects

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 5253 patients, 3289 on duloxetine and 1964 on placebo). The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with ARICLAIM were: nausea; headache, dry mouth and somnolence.

*Table 1: Adverse reactions*

Frequency estimate: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1,000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
<i>Investigations</i>					
	Weight decrease	Weight increase Creatinine phosphokinase increase	Blood cholesterol increased		
<i>Cardiac Disorders</i>					
	Palpitations	Tachycardia	Supra-ventricular arrhythmia, mainly atrial fibrillation		
<i>Nervous System Disorders</i>					
Headache (13.8%) Somnolence (10.7%)	Dizziness Tremor Lethargy Paraesthesia	Dyskinesia Poor quality sleep Nervousness Myoclonus Disturbance in attention Dysgeusia			Serotonin syndrome Convulsions Akathisia Psychomotor restlessness Extra-pyramidal symptoms
<i>Eye Disorders</i>					
	Blurred vision	Visual disturbance Mydriasis	Glaucoma		
<i>Ear and Labyrinth Disorders</i>					
	Tinnitus <sup>1</sup>	Vertigo Ear pain			
<i>Respiratory, thoracic and mediastinal disorders</i>					
	Yawning	Epistaxis Throat tightness			

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
<i>Gastrointestinal Disorders</i>					
Nausea (21.7%) Dry mouth (13.2%)	Diarrhoea Constipation Vomiting Dyspepsia Flatulence	Gastroenteritis Stomatitis Gastritis Eructation	Haematochezia Breath odour		Gastrointestinal haemorrhage
<i>Renals and Urinary Disorders</i>					
		Urinary Retention Urinary hesitation Dysuria Nocturia Polyuria Urine flow decreased			Urine odour abnormal
<i>Skin and Subcutaneous Tissue Disorders</i>					
	Rash Sweating increased Night sweats	Photo-sensitivity reactions Increased tendency to bruise Dermatitis contact Urticaria Cold sweat			Stevens-Johnson Syndrome Angio-neurotic oedema
<i>Musculoskeletal and connective tissue disorders</i>					
	Musculo-skeletal pain Muscle tightness Muscle spasm	Muscle twitching	Trismus		
<i>Endocrine disorders</i>					
			Hypo-thyroidism		
<i>Metabolism and Nutrition Disorders</i>					
	Decreased Appetite	Hyperglycemia (reported especially in diabetic patients)	Dehydration SIADH Hypo-natremia		
<i>Infections and infestations</i>					
		Laryngitis			
<i>Vascular Disorders</i>					
	Flushing	Syncope <sup>2</sup> Orthostatic hypotension <sup>2</sup> Blood pressure increase Peripheral coldness			Hypertensive crisis Hypertension

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
<i>General Disorders and Administration Site Conditions</i>					
	Fatigue Abdominal pain	Feeling hot Malaise Gait disturbance Feeling abnormal Feeling cold Thirst Chills			Chest pain
<i>Immune system disorders</i>					
		Hyper-sensitivity disorder	Anaphylactic reaction		
<i>Hepato-biliary disorders</i>					
		Hepatitis <sup>3</sup> Elevated liver enzymes (ALT, AST, alkaline phosphatase)  Acute liver injury			Hepatic failure Jaundice
<i>Reproductive System and Breast Disorders</i>					
	Erectile dysfunction	Sexual dysfunction Ejaculation disorder Ejaculation delayed Gynaecological haemorrhage	Menopausal symptoms		
<i>Psychiatric Disorders</i>					
	Insomnia Abnormal dreams Anxiety Agitation Libido decreased Orgasm abnormal	Sleep disorder Apathy Disorientation Bruxism	Aggression and anger <sup>5</sup> Mania		Suicidal behaviour <sup>4</sup> Suicidal ideation <sup>4</sup> Hallucinations

<sup>1</sup>Cases of tinnitus have also been reported after treatment discontinuation.

<sup>2</sup> Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.

<sup>3</sup> See section 4.4

<sup>4</sup>Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4)

<sup>5</sup>Cases of aggression and anger have been reported particularly early in treatment of after treatment discontinuation.

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms.

Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Electrocardiograms were obtained from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

#### **4.9 Overdose**

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 4800mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote is known for duloxetine but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

### **5. PHARMACOLOGICAL PROPERTIES**

#### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

Although data from a one-year open label study offer some evidence for longer-term efficacy, no conclusive efficacy data for treatments longer than 12 weeks duration are available from placebo-controlled studies.

## **5.2 Pharmacokinetic properties**

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Duloxetine is well absorbed after oral administration with a C<sub>max</sub> occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). These changes do not have any clinical significance. Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5hydroxy,6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

**Special populations:**

*Gender:* pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximatively 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

*Age:* pharmacokinetic differences have been identified between younger and elderly females ( $\geq 65$  years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

*Renal impairment:* end stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C<sub>max</sub> and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

*Hepatic impairment:* moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

*Nursing mothers:* The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

### 5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine (45 mg/kg/day) before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In prenatal/postnatal toxicity studies in the rat, duloxetine induced adverse behavioural effects in the offspring at exposures below maximum clinical exposure (AUC).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Capsule content:**

Hypromellose.

Hydroxypropyl methylcellulose acetate succinate

Sucrose

Sugar spheres

Talc

Titanium dioxide (E171)

Triethyl citrate.

**Capsule shell:**

30 mg:

Gelatin

Sodium Lauryl Sulfate

Titanium Dioxide (E171)

Indigo Carmine (E132)

Edible Green Ink

Edible Green Ink contains:

Black Iron Oxide-Synthetic (E172)

Yellow Iron Oxide- Synthetic (E172)

Propylene glycol

Shellac.

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Store in the original package in order to protect from moisture. Do not store above 30 C.

**6.5 Nature and contents of container**

Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminum foil.

ARICLAIM 30 mg is available in packs of 7, 28 and 98 capsules.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/283/008

EU/1/04/283/009

EU/1/04/283/010

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**



## **1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 60 mg hard gastro-resistant capsules

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each capsule contains 60 mg of duloxetine (as hydrochloride).

Excipients: sucrose 17.2 mg.

For a full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Hard gastro-resistant capsule.

Opaque green body, imprinted with '60 mg' and an opaque blue cap, imprinted with '9542'.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Treatment of diabetic peripheral neuropathic pain in adults.

### **4.2 Posology and method of administration**

For oral use.

#### *Adults*

The starting and recommended maintenance dose is 60 mg daily with or without food. Dosages above 60 mg once daily, up to a maximum dose of 120 mg per day administered in evenly divided doses, have been evaluated from a safety perspective in clinical trials. The plasma concentration of duloxetine displays large inter-individual variability (see 5.2). Hence, some patients that respond insufficiently to 60 mg may benefit from a higher dose.

The medicinal product response should be evaluated after 2 months' of treatment. Additional response after this time is unlikely (see 5.1).

The therapeutic benefit should regularly (at least every three months) be reassessed.

#### *Elderly*

*Diabetic Peripheral Neuropathic Pain:* No dosage adjustment is recommended for elderly patients solely on the basis of age. However, caution should be exercised when treating the elderly (see section 5.2).

#### *Children and adolescents*

There is no experience in children (see section 4.4).

#### *Hepatic impairment*

ARICLAIM should not be used in patients with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

#### *Renal insufficiency*

No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). ARICLAIM should not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

#### *Discontinuation of treatment*

Abrupt discontinuation should be avoided. When stopping treatment with ARICLAIM the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Concomitant use of ARICLAIM with nonselective, irreversible Monoamine Oxidase Inhibitors (MAOIs) is contraindicated (see section 4.5).

Liver disease resulting in hepatic impairment (see section 5.2).

ARICLAIM should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (i.e. potent CYP1A2 inhibitors) since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with ARICLAIM is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

### **4.4 Special warnings and precautions for use**

#### *Mania and seizures*

ARICLAIM should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

#### *Mydriasis*

Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing ARICLAIM to patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

#### *Blood pressure and heart rate*

Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

### *Renal impairment*

Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

### *Use with antidepressants*

Caution should be exercised when using ARICLAIM in combination with antidepressants. In particular the combination with selective reversible MAOIs is not recommended.

### *St John's wort*

Undesirable effects may be more common during concomitant use of ARICLAIM and herbal preparations containing St John's wort (*Hypericum perforatum*).

### *Depression, suicidal ideation and behaviour*

Although ARICLAIM is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medication. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8). Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on ARICLAIM therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of ARICLAIM is recommended (see Section 4.2).

### *Use in children and adolescents under 18 years of age*

No clinical trials have been conducted with duloxetine in paediatric populations. ARICLAIM should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger), were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

### *Haemorrhage*

There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies.

### *Hyponatremia*

Hyponatremia has been reported rarely, predominantly in the elderly, when administering ARICLAIM. Caution is required in patients at increased risk for hyponatremia; such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics. Hyponatremia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH).

### *Discontinuation of treatment*

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In clinical trials adverse events seen on abrupt treatment discontinuation occurred in approximately 45% of patients treated with ARICLAIM and 23% of patients taking placebo.

The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

#### *Akathisia/psychomotor restlessness*

The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

#### *Medicinal products containing duloxetine*

Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive episodes as well as stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

#### *Hepatitis/increased liver enzymes*

Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

#### *Sucrose*

ARICLAIM gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

### **4.5 Interaction with other medicinal products and other forms of interaction**

*CNS medicinal products:* the risk of using duloxetine in combination with other CNS-active medicinal products has not been systematically evaluated, except in the cases described in this section. Consequently, caution is advised when ARICLAIM is taken in combination with other centrally acting medicinal products and substances including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

*Monoamine Oxidase Inhibitors (MAOIs):* due to the risk of serotonin syndrome, ARICLAIM should not be used in combination with nonselective irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping ARICLAIM before starting an MAOI (see section 4.3).

For selective, reversible MAOIs, like moclobemide, the risk of serotonin syndrome is lower. However, the concomitant use of ARICLAIM with selective, reversible MAOIs is not recommended (see section 4.4).

*Serotonin syndrome:* in rare cases, serotonin syndrome has been reported in patients using SSRIs (e.g. paroxetine, fluoxetine) concomitantly with serotonergic medicinal products. Caution is advisable if

ARICLAIM is used concomitantly with serotonergic antidepressants like SSRIs, tricyclics like clomipramine or amitriptyline, St John's wort (*Hypericum perforatum*), venlafaxine or triptans, tramadol, pethidine and tryptophan.

#### *Effect of duloxetine on other medicinal products*

*Medicinal products metabolised by CYP1A2:* The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).

*Medicinal products metabolised by CYP2D6:* Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if ARICLAIM is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

*Oral contraceptives and other steroidal agents:* results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

*Anticoagulants and antiplatelet agents:* Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding. Furthermore, increases in INR values have been reported when duloxetine was co-administered with warfarin.

#### *Effects of other medicinal products on duloxetine*

*Antacids and H<sub>2</sub> antagonists:* co-administration of duloxetine with aluminium- and magnesium-containing antacids or duloxetine with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

*Inhibitors of CYP 1A2:* because CYP1A2 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC<sub>0-t</sub> 6-fold. Therefore ARICLAIM should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

*Inducers of CYP1A2:* Population pharmacokinetic analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

## **4.6 Pregnancy and lactation**

### *Pregnancy*

There are no data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (see section 5.3).

The potential risk for humans is unknown. As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. ARICLAIM should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.

### *Breast feeding*

Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of ARICLAIM while breast-feeding is not recommended.

## **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed. ARICLAIM may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

## **4.8 Undesirable effects**

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials (comprising a total of 5253 patients, 3289 on duloxetine and 1964 on placebo). The most commonly observed adverse reactions in patients with diabetic neuropathic pain treated with ARICLAIM were: nausea; headache, dry mouth and somnolence.

*Table 1: Adverse reactions*

Frequency estimate: Very common ( $\geq 1/10$ ), common ( $\geq 1/100$  and  $< 1/10$ ), uncommon ( $\geq 1/1,000$  and  $< 1/100$ ), rare ( $\geq 1/10,000$  and  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

<b>Very common</b>	<b>Common</b>	<b>Uncommon</b>	<b>Rare</b>	<b>Very Rare</b>	<b>Frequency not known</b>
<i>Investigations</i>					
	Weight decrease	Weight increase Creatinine phosphokinase increase	Blood cholesterol increased		
<i>Cardiac Disorders</i>					
	Palpitations	Tachycardia	Supra-ventricular arrhythmia, mainly atrial fibrillation		
<i>Nervous System Disorders</i>					
Headache (13.8%) Somnolence (10.7%)	Dizziness Tremor Lethargy Paraesthesia	Dyskinesia Poor quality sleep Nervousness Myoclonus Disturbance in attention Dysgeusia			Serotonin syndrome Convulsions Akathisia Psychomotor restlessness Extra-pyramidal symptoms
<i>Eye Disorders</i>					
	Blurred vision	Visual disturbance Mydriasis	Glaucoma		
<i>Ear and Labyrinth Disorders</i>					

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
	Tinnitus <sup>1</sup>	Vertigo Ear pain			
<i>Respiratory, thoracic and mediastinal disorders</i>					
	Yawning	Epistaxis Throat tightness			
<i>Gastrointestinal Disorders</i>					
Nausea (21.7%) Dry mouth (13.2%)	Diarrhoea Constipation Vomiting Dyspepsia Flatulence	Gastroenteritis Stomatitis Gastritis Eructation	Haematochezia Breath odour		Gastrointestinal haemorrhage
<i>Renals and Urinary Disorders</i>					
		Urinary Retention Urinary hesitation Dysuria Nocturia Polyuria Urine flow decreased			Urine odour abnormal
<i>Skin and Subcutaneous Tissue Disorders</i>					
	Rash Sweating increased Night sweats	Photo-sensitivity reactions Increased tendency to bruise Dermatitis contact Urticaria Cold sweat			Stevens-Johnson Syndrome Angio-neurotic oedema
<i>Muscoskeletal and connective tissue disorders</i>					
	Musculo-skeletal pain Muscle tightness Muscle spasm	Muscle twitching	Trismus		
<i>Endocrine disorders</i>					
			Hypo-thyroidism		
<i>Metabolism and Nutrition Disorders</i>					
	Decreased Appetite	Hyperglycemia (reported especially in diabetic patients)	Dehydration SIADH Hypo-natremia		
<i>Infections and infestations</i>					
		Laryngitis			
<i>Vascular Disorders</i>					
	Flushing	Syncope <sup>2</sup> Orthostatic			Hypertensive crisis

Very common	Common	Uncommon	Rare	Very Rare	Frequency not known
		hypotension <sup>2</sup> Blood pressure increase Peripheral coldness			Hypertension
<i>General Disorders and Administration Site Conditions</i>					
	Fatigue Abdominal pain	Feeling hot Malaise Gait disturbance Feeling abnormal Feeling cold Thirst Chills			Chest pain
<i>Immune system disorders</i>					
		Hyper-sensitivity disorder	Anaphylactic reaction		
<i>Hepato-biliary disorders</i>					
		Hepatitis <sup>3</sup> Elevated liver enzymes (ALT, AST, alkaline phosphatase)  Acute liver injury			Hepatic failure Jaundice
<i>Reproductive System and Breast Disorders</i>					
	Erectile dysfunction	Sexual dysfunction Ejaculation disorder Ejaculation delayed Gynaecological haemorrhage	Menopausal symptoms		
<i>Psychiatric Disorders</i>					
	Insomnia Abnormal dreams Anxiety Agitation Libido decreased Orgasm abnormal	Sleep disorder Apathy Disorientation Bruxism	Aggression and anger <sup>5</sup> Mania		Suicidal behaviour <sup>4</sup> Suicidal ideation <sup>4</sup> Hallucinations

<sup>1</sup> Cases of tinnitus have also been reported after treatment discontinuation.

<sup>2</sup> Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.

<sup>3</sup> See section 4.4



<sup>4</sup>Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4)

<sup>5</sup>Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia), sleep disturbances (including insomnia and intense dreams), agitation or anxiety, nausea and/or vomiting, tremor, headache, irritability, diarrhoea, hyperhidrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Electrocardiograms were obtained from 528 duloxetine-treated and 205 placebo-treated patients with diabetic neuropathic pain in clinical trials lasting up to 13-weeks. The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

## **4.9 Overdose**

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 4800mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote is known for duloxetine but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. Duloxetine dose-dependently increases extracellular levels of serotonin and noradrenaline in various brain areas of animals.

Duloxetine normalised pain thresholds in several preclinical models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of potentiation of descending inhibitory pain pathways within the central nervous system.

The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 randomised, 12-week, double-blind, placebo-controlled, fixed dose studies in adults (22 to 88 years) having diabetic neuropathic pain for at least 6 months. Patients meeting diagnostic criteria for major depressive disorder were excluded from these trials. The primary outcome measure was the weekly mean of 24-hour average pain, which was collected in a daily diary by patients on an 11-point Likert scale.

In both studies, duloxetine 60 mg once daily and 60 mg twice daily significantly reduced pain compared with placebo. The effect in some patients was apparent in the first week of treatment. The difference in mean improvement between the two active treatment arms was not significant. At least 30% reported pain reduction was recorded in approximately 65% of duloxetine treated patients versus 40% for placebo. The corresponding figures for at least 50% pain reduction were 50% and 26% respectively. Clinical response rates (50% or greater improvement in pain) were analysed according to whether or not the patient experienced somnolence during treatment. For patients not experiencing somnolence, clinical response was observed in 47% of patients receiving duloxetine and 27% patients on placebo. Clinical response rates in patients experiencing somnolence were 60% on duloxetine and 30% on placebo. Patients not demonstrating a pain reduction of 30% within 60 days of treatment were unlikely to reach this level during further treatment.

Although data from a one-year open label study offer some evidence for longer-term efficacy, no conclusive efficacy data for treatments longer than 12 weeks duration are available from placebo-controlled studies.

## **5.2 Pharmacokinetic properties**

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Duloxetine is well absorbed after oral administration with a C<sub>max</sub> occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). These changes do not have any clinical significance. Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulphate conjugate of 5hydroxy,6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

### **Special populations:**

*Gender:* pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of

clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

*Age:* pharmacokinetic differences have been identified between younger and elderly females ( $\geq 65$  years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

*Renal impairment:* end stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C<sub>max</sub> and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

*Hepatic impairment:* moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic insufficiency.

*Nursing mothers:* The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 µg/day while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics

### 5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine (45 mg/kg/day) before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In prenatal/postnatal toxicity studies in the rat, duloxetine induced adverse behavioural effects in the offspring at exposures below maximum clinical exposure (AUC).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### Capsule content:

Hypromellose.  
Hydroxypropyl methylcellulose acetate succinate  
Sucrose  
Sugar spheres  
Talc  
Titanium dioxide (E171)  
Triethyl citrate.

#### Capsule shell:

60 mg:

Gelatin  
Sodium Lauryl Sulfate  
Titanium Dioxide (E171)  
Indigo Carmine (E132)  
Yellow Iron Oxide (E172)  
Edible White Ink

Edible White Ink contains:  
Titanium Dioxide (E171)  
Propylene glycol  
Shellac  
Povidone.

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

3 years.

## **6.4 Special precautions for storage**

Store in the original package in order to protect from moisture. Do not store above 30 C.

## **6.5 Nature and contents of container**

Polyvinylchloride (PVC), Polyethylene (PE), and Polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminum foil.

ARICLAIM 60 mg is available in packs of 28 and 98 capsules.

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal**

No special requirements.

## **7. MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

## **8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/283/011  
EU/1/04/283/012

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

## **10. DATE OF REVISION OF THE TEXT**

## **ANNEX II**

- A. MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE  
FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

**A     MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release

Lilly S.A.  
Avda. de la Industria N° 30,  
28108 Alcobendas  
Madrid  
Spain

**B     CONDITIONS OF THE MARKETING AUTHORISATION**

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**



**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTONS FOR 40 MG HARD GASTRO-RESISTANT CAPSULES**

**1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 40 mg, hard gastro-resistant capsules.  
Duloxetine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 40 mg duloxetine (as hydrochloride)

**3. LIST OF EXCIPIENTS**

Contains sucrose  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

28 hard gastro-resistant capsules  
56 hard gastro-resistant capsules  
98 hard gastro-resistant capsules  
140 hard gastro-resistant capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}.

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package. Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/283/002-005

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

ARICLAIM 40 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON FOR 98 CAPSULES (40 MG) AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 40 mg hard gastro-resistant capsules  
Duloxetine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 40 mg duloxetine (as hydrochloride).

**3. LIST OF EXCIPIENTS**

Contains sucrose.  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

98 capsules  
Component of a multipack comprising 2 packs, each containing 98 capsules.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package. Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/283/004

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

ARICLAIM 40 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING  
OUTER WRAPPER LABEL ON MULTIPACKS (2X98 CAPSULES, 40 MG) WRAPPED IN  
FOIL (INCLUDING BLUE BOX)**

**1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 40 mg hard gastro-resistant capsules  
Duloxetine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 40 mg duloxetine (as hydrochloride).

**3. LIST OF EXCIPIENTS**

Contains sucrose  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

Multipack comprising 2 packs, each containing 98 capsules.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT  
OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP {MM/YYYY}

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package. Do not store above 30 °C.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/283/006

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

ARICLAIM 40 mg

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS (40 mg hard gastro-resistant capsules)</b>
---

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

ARICLAIM 40 mg hard gastro-resistant capsules  
Duloxetine

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Lilly

<b>3. EXPIRY DATE</b>
-----------------------

<EXP {MM/YYYY}.

<b>4. BATCH NUMBER</b>
------------------------

Lot:

<b>5. OTHER</b>
-----------------

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTONS FOR 20 MG HARD GASTRO-RESISTANT CAPSULES****1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 20 mg, hard gastro-resistant capsules.  
Duloxetine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 20 mg duloxetine (as hydrochloride).

**3. LIST OF EXCIPIENTS**

Contains sucrose.  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

28 hard gastro-resistant capsules  
56 hard gastro-resistant capsules.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the leaflet before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP {MM/YYYY}.

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package. Do not store above 30 °C.



**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/04/283/001

EU/1/04/283/007

**13. BATCH NUMBER**

Lot:

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

ARICLAIM 20 mg

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS (20 mg hard gastro-resistant capsules)</b>
---

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

ARICLAIM 20 mg hard gastro-resistant capsules  
Duloxetine

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Lilly

<b>3. EXPIRY DATE</b>
-----------------------

<EXP {MM/YYYY}.

<b>4. BATCH NUMBER</b>
------------------------

Lot:

<b>5. OTHER</b>
-----------------

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTONS FOR 30 MG HARD GASTRO-RESISTANT CAPSULES**

**1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 30 mg, hard gastro-resistant capsules.  
Duloxetine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 30 mg of duloxetine (as hydrochloride)

**3. LIST OF EXCIPIENTS**

Contains sucrose  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

7 hard gastro-resistant capsules,  
28 hard gastro-resistant capsules  
98 hard gastro-resistant capsules

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package. Do not store above 30°C

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/04/283/008

EU/1/04/283/009

EU/1/04/283/010

<b>13. BATCH NUMBER</b>
-------------------------

Lot:

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

Medicinal product subject to medical prescription.

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
-----------------------------------

ARICLAIM 30 mg

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b> <b>30 mg hard gastro-resistant capsules</b>
---

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

ARICLAIM 30 mg hard gastro-resistant capsules  
Duloxetine

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Lilly

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot:

<b>5. OTHER</b>
-----------------

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING****CARTONS FOR 60 MG HARD GASTRO-RESISTANT CAPSULES****1. NAME OF THE MEDICINAL PRODUCT**

ARICLAIM 60 mg, hard gastro-resistant capsules.  
Duloxetine

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each capsule contains 60 mg of duloxetine (as hydrochloride)

**3. LIST OF EXCIPIENTS**

Contains sucrose  
See leaflet for further information

**4. PHARMACEUTICAL FORM AND CONTENTS**

28, hard gastro-resistant capsules  
98, hard gastro-resistant capsules.

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Oral use.  
Read the leaflet before use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY****8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in the original package. Do not store above 30°C

<b>10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE</b>
--

<b>11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER</b>
---

Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA, Houten, The Netherlands.

<b>12. MARKETING AUTHORISATION NUMBER(S)</b>
--

EU/1/04/283/011

EU/1/04/283/012

<b>13. BATCH NUMBER</b>
-------------------------

Lot:

<b>14. GENERAL CLASSIFICATION FOR SUPPLY</b>
--

Medicinal product subject to medical prescription.

<b>15. INSTRUCTIONS ON USE</b>
--------------------------------

<b>16. INFORMATION IN BRAILLE</b>
-----------------------------------

ARICLAIM 60 mg

<b>MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS</b> <b>60 mg hard gastro-resistant capsules</b>
---

<b>1. NAME OF THE MEDICINAL PRODUCT</b>
---

ARICLAIM 60 mg hard gastro-resistant capsules  
Duloxetine

<b>2. NAME OF THE MARKETING AUTHORISATION HOLDER</b>
--

Lilly

<b>3. EXPIRY DATE</b>
-----------------------

EXP

<b>4. BATCH NUMBER</b>
------------------------

Lot:

<b>5. OTHER</b>
-----------------



## **B. PACKAGE LEAFLET**

## **PACKAGE LEAFLET: INFORMATION FOR THE USER**

### **ARICLAIM 40 mg hard gastro-resistant capsules ARICLAIM 20 mg hard gastro-resistant capsules Duloxetine (as hydrochloride)**

#### **Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What ARICLAIM is and what it is used for
2. Before you take ARICLAIM
3. How to take ARICLAIM
4. Possible side effects
5. How to store ARICLAIM
6. Further information

## **1. WHAT ARICLAIM IS AND WHAT IT IS USED FOR**

ARICLAIM increases the levels of serotonin and norepinephrine in the nervous system. ARICLAIM is a medicine to be taken by mouth to treat Stress Urinary Incontinence (SUI) in women or to treat a condition called diabetic neuropathic pain in adults.

Stress urinary incontinence is a medical condition in which patients have accidental loss or leakage of urine during physical exertion or activities such as laughing, coughing, sneezing, lifting, or exercise.

ARICLAIM is believed to work by increasing the strength of the muscle that holds back urine when you laugh, sneeze, or perform physical activities.

The efficacy of ARICLAIM is reinforced when combined with a training program called Pelvic Floor Muscle Training (PFMT).

Neuropathic pain is a medical condition in which the pain is commonly described as burning, stabbing, stinging, shooting or aching or like an electric shock. There may be loss of feeling in the affected area, or sensations such as touch, heat, cold or pressure may cause pain.

The effect of ARICLAIM may be noticeable in many patients with diabetic neuropathic pain within 1 week of treatment.

## **2. BEFORE YOU TAKE ARICLAIM**

#### **Do not take ARICLAIM**

- If you are allergic (hypersensitive) to duloxetine or any of the inactive ingredients of ARICLAIM.
- If you are taking or have taken within the last 14 days, another medicine known as a monoamine oxidase inhibitor - MAOI (see section below 'Taking other medicines').
- If you have liver disease.
- If you are taking fluvoxamine which is usually used to treat depression, ciprofloxacin or enoxacin which are used to treat some infections.

- If you have severe kidney disease.
- If you suffer from uncontrolled high blood pressure.

### **Take special care with ARICLAIM**

The following are reasons why ARICLAIM may not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine:

- You are taking other medicines to treat depression.
- You are taking a herbal treatment containing St. John's Wort (*Hypericum perforatum*).
- You have kidney disease.
- You have had seizures (fits).
- You suffer from or have suffered from mania or bipolar disorder.
- You have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
- You have a history of bleeding disorders (tendency to develop bruises).
- You are at risk of low sodium levels.
- You have high blood pressure.
- You are currently being treated with another medicine which may cause liver damage.
- You are taking other medicines containing duloxetine.
- You have intolerance to some sugars (see below).
- You are considering stopping ARICLAIM (see section 3).

ARICLAIM may cause a sensation of restlessness or an inability to sit or stand still. You should tell your doctor if this happens to you.

*Thoughts of suicide and worsening of your depression or anxiety disorder* If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

### *Use in children and adolescents under 18 years of age*

ARICLAIM should not be used for children and adolescents under the age of 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Also, the long-term safety effects concerning growth, maturation, and cognitive and behavioural development of ARICLAIM in this age group have not yet been demonstrated.

### **Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. The main ingredient of ARICLAIM, duloxetine, is used in other medicines for other conditions (depression and urinary incontinence). Using more than one of these medicines at the same time should be avoided. Check with your doctor if you are already taking other medicines containing duloxetine.

Your doctor should decide whether you can take ARICLAIM with other medicines. Do not start or stop taking any medicines, including those bought without a prescription and herbal remedies, before checking with your doctor.

*Monoamine Oxidase Inhibitors (MAOI):* you should not take ARICLAİM with an MAOI or within 14 days of stopping an MAOI. Taking an MAOI together with many prescription medicines, including ARICLAİM, can cause serious or even life-threatening side effects. You must wait at least 14 days after you have stopped taking an MAOI before you can take ARICLAİM. Also, you need to wait at least 5 days after you stop taking ARICLAİM before you take an MAOI.

*CNS medicines:* caution is advised when ARICLAİM is taken in combination with other centrally acting medicines or substances, including alcohol and sedative medicines (benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines). Inform your doctor if you are taking any of these medicines.

*Serotonin syndrome:* you should tell your doctor if you are taking any of the medicines that act in a similar way to duloxetine. Examples of these medicines include: triptans, tramadol, tryptophan, certain antidepressants: SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline) and venlafaxine. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ARICLAİM, you should see your doctor.

*Oral -anticoagulants:* You should tell your doctor if you are taking oral –anticoagulants (medicines which thin the blood). These medicines might increase the risk of bleeding.

### **Taking ARICLAİM with food and drink**

ARICLAİM may be taken with or without food. You should take extra care if you drink alcohol while taking ARICLAİM.

### **Pregnancy and breast-feeding**

Tell your doctor if you become pregnant, or you are trying to become pregnant, while you are taking ARICLAİM. You should use ARICLAİM only after discussing the potential benefits and any potential risks to your unborn child with your doctor.

You should ask your doctor or pharmacist for advice if you are breast-feeding. The use of ARICLAİM while breastfeeding is not recommended.

Ask your doctor or pharmacist for advice before taking any medicine.

### **Driving and using machines**

ARICLAİM may make you feel sleepy or dizzy. Do not drive or use any tools or machines until you know how ARICLAİM affects you.

### **Important information about some of the ingredients of ARICLAİM**

ARICLAİM contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## **3. HOW TO TAKE ARICLAİM**

Always take ARICLAİM exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The recommended dose of ARICLAİM for the treatment of Stress Urinary Incontinence is 40 mg twice a day (in the morning and late afternoon/evening). Your doctor may decide to start your treatment with one capsule of 20 mg twice a day for two weeks before increasing the dose to 40 mg twice a day.

The usual dose of ARICLAİM for the treatment of Neuropathic pain is 60 mg once a day, but your doctor will prescribe the dose that is right for you.

ARICLAİM is for oral use. You should swallow your capsule whole with a drink of water.

To help you remember to take ARICLAIM, you may find it easier to take it at the same times every day.

Do not stop taking ARICLAIM without talking to your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**If you take more ARICLAIM than you should**

Call your doctor or pharmacist immediately if you take more than the amount of ARICLAIM prescribed by your doctor.

**If you forget to take ARICLAIM**

Do not take a double dose to make up for forgotten doses.

If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only a single dose as usual. Do not take more than the daily amount of ARICLAIM that has been prescribed for you in one day.

**If you stop taking ARICLAIM**

Do not stop taking your capsules without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need ARICLAIM he will ask you to reduce your dose over 2 weeks. Some patients, who suddenly stop taking ARICLAIM after more than 1 week of therapy, have had symptoms such as dizziness, tingling feelings like pins and needles, sleep disturbances (vivid dreams, nightmares, inability to sleep), feeling restless or agitated, feeling anxious, feeling sick (nausea) or being sick (vomiting), tremor (shakiness), headaches, feeling irritable, diarrhoea, excessive sweating or vertigo. . These symptoms are usually not serious and disappear within a few days, but if you have symptoms that are troublesome you should ask your doctor for advice.

#### **4. POSSIBLE SIDE EFFECTS**

Like all medicines, ARICLAIM can cause side effects, although not everybody gets them. These effects are normally mild to moderate and often disappear after a short time.

**Very common side effects (these can affect more than 1 in 10 patients treated)with ARICLAIM when taken to treat stress urinary incontinence**

Feeling sick (nausea), dry mouth, and tiredness.

**Very common side effects (these can affect more than 1 in 10 patients treated)with ARICLAIM when taken to treat diabetic neuropathic pain**

Feeling sick (nausea), somnolence, headache, dizziness and constipation.

**Common side effects (these can affect from 1 to 10 users in 100 patients treated)**

- Anxiety, having abnormal dreams.
- Dizziness, tremor or numbness, including numbness or tingling of the skin.
- Being sick (vomiting), heartburn or breaking wind, lack of appetite.
- Blurred eyesight.
- Feeling the heart pumping in the chest or hot flushes.
- Problems getting an erection, changes in orgasm or less sex drive.
- (itchy) Rash.
- Muscle pain, muscle tightness or muscle spasm.

**Uncommon side effects (these can affect from 1 to 10 users in 1,000 patients treated)**

- Throat inflammation.
- Feeling agitated, feeling disorientated, feeling sleepy, having a poor quality of sleep, lack of motivation or increased yawning.

- Tasting things differently than usual, disturbance in attention or spasms and involuntary movements of the muscles.
- Weight loss or weight gain, burping, indigestion or gastroenteritis.
- Inflammation of the liver that may cause abdominal pain, tiredness or yellow coloration of the skin.
- Vertigo, tinnitus ( perception of sound in the ear when there is no external sound, ear pain.
- Larger pupils (the dark centre of the eye) or visual disturbance.
- Flushing, increase in blood pressure, feeling cold in your fingers and/or toes, feeling dizzy ( particularly when standing up too quickly), fast or irregular heart beat, night sweats, cold sweats, shivering or fainting.
- Changes in ejaculation, abnormal periods, including heavy or prolonged periods
- Allergic reactions, increased tendency to bruise, blisters or sensitivity to sunlight.
- Muscle twitching.
- Need to pass urine during the night or difficulty or inability to pass urine.
- Grinding of teeth, dehydration, feeling hot/cold, thirst, throat tightness or nose bleeds
- Increased level of cholesterol in the blood.

**Rare side effects (these can affect from 1 to 10 users in 10,000 patients treated)**

- Mania (a disorder which symptoms are over activity, racing thoughts and decrease need for sleep), experiencing hallucinations
- Increased level of sugar in the blood, low levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused), syndrome of inadequate secretion of anti-diuretic hormone (SIADH).
- Bad breath.
- Increased pressure in the eye.
- Menopausal symptoms.
- Sexual problems.
- Abnormal manner of walking, contraction of the jaw muscle.
- Decrease of activity of the thyroid gland, chest or stomach pain.
- Need to pass more urine than usual or urine flow decreased.

**Other possible side effects**

- Experiencing aggression and anger suicidal thoughts or behaviour.
- A sensation of restlessness or an inability to sit or stand still, “Serotonin syndrome” (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), fits or stiffness.
- Passing bright red blood in your stools vomiting blood, or black tarry stools (faeces).
- Abnormal urine odour.
- Yellow colouration of the skin (jaundice), hepatic failure, Stevens-Johnson syndrome, sudden swelling of skin of mucosa (angioedema).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE ARICLAIM

### Keep out of the reach and sight of children

Do not use ARICLAIM after the expiry date which is stated on the carton.

Store in the original pack. Do not store above 30 °C.

## 6. FURTHER INFORMATION

### What ARICLAIM contains

The active substance is duloxetine. Each capsule contains 20 or 40 mg of duloxetine (as hydrochloride).

The other ingredients are:

Capsule content: hypromellose, hydroxypropyl methylcellulose acetate succinate, sucrose, sugar spheres, talc, titanium dioxide (E171), triethyl citrate.

Capsule shell: gelatin, sodium lauryl sulphate, titanium dioxide (E171), indigo carmine (E132), iron oxide red and iron oxide yellow, edible black ink.

Edible Ink: Black Iron Oxide-Synthetic (E172), Propylene glycol, Shellac.

### What ARICLAIM looks like and contents of the pack

ARICLAIM is a hard gastro-resistant capsule.

Each capsule of ARICLAIM contains pellets of the active substance with a covering to protect them from stomach acid.

ARICLAIM is available in 2 strengths: 20 and 40 mg.

The 40 mg capsule has an opaque orange body imprinted with '40 mg' and an opaque blue cap, imprinted with '9545'.

The 20 mg capsule has an opaque blue body imprinted with '20 mg' and an opaque blue cap, imprinted with '9544'.

ARICLAIM 40 mg is available in blister packs of 28, 56, 98, 140 and 196 (2 x 98) capsules.

ARICLAIM 20 mg is available in blister packs of 28 and 56 capsules.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Marketing Authorisation Holder: Eli Lilly Nederland BV, Grootslag 1-5, NL-3991 RA Houten, The Netherlands.

Manufacturer: Lilly S.A., Avda. De la Industria, 30, 28108 Alcobendas, Madrid, Spain.

For any information about this medicine product, please contact the local representative of the Marketing Authorisation Holder.

#### België/Belgique/Belgien

S.C.S. Boehringer Ingelheim Comm.V.

Tél/Tel: +32 27 73 33 11

#### България

ТП "Ели Лили Недерланд" Б.В. - България

тел. + 359 2 491 41 40

#### Česká republika

Boehringer Ingelheim spol. s r.o.

Tel.: + 42 02 34 65 51 11

#### Luxembourg/Luxemburg

S.C.S. Boehringer Ingelheim Comm.V.

Tél/Tel: +32 2 773 33 11

#### Magyarország

Boehringer Ingelheim Pharma

Tel.: +36 1 224 7120

#### Malta

Boehringer Ingelheim Ltd.

Tel: +356 25600 500

**Danmark**

Boehringer Ingelheim Danmark A/S

Tlf: +45 39 15 88 88

**Deutschland**

Boehringer Ingelheim Pharma GmbH & Co. KG

Tel: +49 (0) 69 50 50 83 09

**Eesti**

Boehringer Ingelheim Pharma GmbH

Tel: + 37 2 60 80 940

**Ελλάδα**

ΦΑΡΜΑΣΕΠΒ-ΛΙΑΛΥ Α.Ε.Β.Ε.

Τηλ: +30 210 629 4600

**España**

Dista S.A..

Tel: + 34 91 623 17 32

**France**

Boehringer Ingelheim France S.A.S.

Tél: +33 3 26 50 45 33

**Ireland**

Boehringer Ingelheim Ireland Ltd.

Tel: +353-(0) 1 661 4377

**Ísland**

Eli Lilly Danmark A/S, Útibú á Íslandi

Tel: + 354 520 34 00

**Italia**

Eli Lilly Italia S.p.A.

Tel: + 39- 055 42571

**Κύπρος**

Boehringer Ingelheim Ellas A.E.

Τηλ: +30 2 10 89 06 300

**Latvija**

Boehringer Ingelheim Pharma GmbH

Tel: +37 167 24 00 68

**Lietuva**

Boehringer Ingelheim Pharma Ges mbH

Tel.: +370 37 47 39 22

**Nederland**

Boehringer Ingelheim b.v.

Tel: +31 30 6 02 59 14

**Norge**

Boehringer Ingelheim Norway KS

Tlf: +47 66 76 13 00

**Österreich**

Boehringer Ingelheim Austria GmbH

Tel: +43 1 710 3739

**Polska**

Boehringer Ingelheim Sp.z o.o.

Tel.: +48 22 699 0 699

**Portugal**

Boehringer Ingelheim, Lda

Tel: +351 21 313 53 00

**România**

Eli Lilly România S.R.L.

Tel: + 40 21 4023000

**Slovenija**

Boehringer Ingelheim Pharma

Tel.: +386 1 586 40 00

**Slovenská republika**

Boehringer Ingelheim Pharma

Tel.: +421 2 5341 8445

**Suomi/Finland**

Oy Eli Lilly Finland Ab

Puh/Tel: +358 9 8545 250

**Sverige**

Boehringer Ingelheim AB

Tel: +46 8 721 21 00

**United Kingdom**

Boehringer Ingelheim Ltd.

Tel: +44 (0) 1256 315999

**This leaflet was last approved in**

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.ema.europa.eu>.



## **PACKAGE LEAFLET: INFORMATION FOR THE USER**

### **ARICLAIM 30 mg hard gastro-resistant capsules ARICLAIM 60 mg hard gastro-resistant capsules Duloxetine (as hydrochloride)**

#### **Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

#### **In this leaflet:**

1. What ARICLAIM is and what it is used for
2. Before you take ARICLAIM
3. How to take ARICLAIM
4. Possible side effects
5. How to store ARICLAIM
6. Further information

## **1. WHAT ARICLAIM IS AND WHAT IT IS USED FOR**

ARICLAIM increases the levels of serotonin and norepinephrine in the nervous system.

ARICLAIM is used in adults to treat a condition called diabetic neuropathic pain.

Neuropathic pain is a medical condition in which the pain is commonly described as burning, stabbing, stinging, shooting or aching or like an electric shock. There may be loss of feeling in the affected area, or sensations such as touch, heat, cold or pressure may cause pain.

The effect of ARICLAIM may be noticeable in many patients with diabetic neuropathic pain within 1 week of treatment.

## **2. BEFORE YOU TAKE ARICLAIM**

### **Do not take ARICLAIM**

- If you are allergic (hypersensitive) to duloxetine or any of the other ingredients of ARICLAIM.
- If you are taking or have recently taken within the last 14 days, another antidepressant medicine called a monoamine oxidase inhibitor (MAOI) (see also below in section: ‘Taking other medicines’).
- If you have liver disease.
- If you have severe kidney disease.
- If you are taking fluvoxamine which is usually used to treat depression, ciprofloxacin or enoxacin which are used to treat some infections.
- If you suffer from uncontrolled high blood pressure.

### **Take special care with ARICLAIM**

The following are reasons why ARICLAIM may not be suitable for you. If any of them apply to you, talk to your doctor before you take the medicine:

- You are taking other medicines to treat depression.
- You are taking a herbal treatment containing St. John’s Wort (*Hypericum perforatum*).

- You have kidney disease.
- You have had seizures (fits).
- You suffer from or have suffered from mania or bipolar disorder.
- You have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
- You have a history of bleeding disorders (tendency to develop bruises).
- You are at risk of low sodium levels.
- You have high blood pressure.
- You are currently being treated with another medicine which may cause liver damage.
- You are taking other medicines containing duloxetine.
- You have intolerance to some sugars (see below).
- You are considering stopping ARICLAIM (see section 3).

ARICLAIM may cause a sensation of restlessness or an inability to sit or stand still. You should tell your doctor if this happens to you.

*Thoughts of suicide and worsening of your depression or anxiety disorder* If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

You may be more likely to think like this:

- If you have previously had thoughts about killing or harming yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

#### *Use in children and adolescents under 18 years of age*

ARICLAIM should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe ARICLAIM for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed ARICLAIM for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking ARICLAIM. Also, the long-term safety effects concerning growth, maturation, and cognitive and behavioural development of ARICLAIM in this age group have not yet been demonstrated.

#### **Taking other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. The main ingredient of ARICLAIM, duloxetine, is used in other medicines for other conditions (depression and urinary incontinence). Using more than one of these medicines at the same time should be avoided. Check with your doctor if you are already taking other medicines containing duloxetine.

Your doctor should decide whether you can take ARICLAIM with other medicines. Do not start or stop taking any medicines, including those bought without a prescription and herbal remedies, before checking with your doctor.

*Monoamine Oxidase Inhibitors (MAOIs):* You should not take ARICLAIM if you are taking, or have recently taken within the last 14 days, another antidepressant medicine called a monoamine oxidase inhibitor (MAOI). Taking a MAOI together with many prescription medicines, including ARICLAIM, can cause serious or even life-threatening side effects. You must wait at least 14 days

after you have stopped taking an MAOI before you can take ARICLAIM. Also, you need to wait at least 5 days after you stop taking ARICLAIM before you take a MAOI.

*Medicines that cause sleepiness:* Tell your doctor if you are taking any medicines which cause you to be sleepy. These would include medicines prescribed by your doctor including benzodiazepines, strong painkillers, antipsychotics, phenobarbital, antihistamines.

*Serotonin syndrome:* you should tell your doctor if you are taking any of the medicines that act in a similar way to duloxetine. Examples of these medicines include: triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine. These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ARICLAIM, you should see your doctor.

*Oral -anticoagulants:* You should tell your doctor if you are taking oral -anticoagulants (medicines which thin the blood). These medicines might increase the risk of bleeding.

### **Taking ARICLAIM with food and drink**

ARICLAIM may be taken with or without food. Care should be taken if you drink alcohol while you are being treated with ARICLAIM.

### **Pregnancy and breast-feeding**

Tell your doctor if you become pregnant, or you are trying to become pregnant, while you are taking ARICLAIM. You should use ARICLAIM only after discussing the potential benefits and any potential risks to your unborn child with your doctor.

You should ask your doctor or pharmacist for advice if you are breast-feeding. The use of ARICLAIM while breastfeeding is not recommended.

Ask your doctor or pharmacist for advice before taking any medicine.

### **Driving and using machines**

ARICLAIM may make you feel sleepy or dizzy. Do not drive or use any tools or machines until you know how ARICLAIM affects you.

### **Important information about some of the ingredients of ARICLAIM**

ARICLAIM contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

## **3. HOW TO TAKE ARICLAIM**

Always take ARICLAIM exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose of ARICLAIM is 60 mg once a day, but your doctor will prescribe the dose that is right for you.

ARICLAIM is for oral use. You should swallow your capsule whole with a drink of water.

To help you remember to take ARICLAIM, you may find it easier to take it at the same times every day.

Talk with your doctor about how long you should keep taking ARICLAIM. Do not stop taking ARICLAIM without talking to your doctor.

### **If you take more ARICLAIM than you should**

Call your doctor or pharmacist immediately if you take more than the amount of ARICLAIM prescribed by your doctor.

### **If you forget to take ARICLAIM**

Do not take a double dose to make up for a forgotten dose.

If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only a single dose as usual. Do not take more than the daily amount of ARICLAIM that has been prescribed for you in one day.

### **If you stop taking ARICLAIM**

Do not stop taking your capsules without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need ARICLAIM he will ask you to reduce your dose over at least 2 weeks before stopping treatment altogether. Some patients who stop taking ARICLAIM suddenly have had symptoms such as dizziness, tingling feelings like pins and needles, sleep disturbances (vivid dreams, nightmares, inability to sleep), feeling restless or agitated, feeling anxious, feeling sick (nausea) or being sick (vomiting), tremor (shakiness), headaches, feeling irritable, diarrhoea, excessive sweating or vertigo. These symptoms are usually not serious and disappear within a few days, but if you have symptoms that are troublesome you should ask your doctor for advice.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

## **4. POSSIBLE SIDE EFFECTS**

Like all medicines, ARICLAIM can cause side effects, although not everybody gets them. These effects are normally mild to moderate and often disappear after a few weeks.

### **Very common side effects (these can affect more than 10 in 100 patients treated)**

Feeling sick (nausea), somnolence, headache or dizziness.

### **Very common side effects (these can affect more than 1 in 10 patients treated)**

Feeling sick (nausea), headache, dry mouth, and feeling sleepy.

### **Common side effects (these can affect from 1 to 10 users in 100 patients treated)**

- Tiredness, trouble sleeping, anxiety, feeling agitated or having abnormal dreams.
- Dizziness, tremor or numbness, including numbness or tingling of the skin.
- Diarrhoea, constipation, being sick (vomiting), heartburn, breaking wind, stomach pain.
- Tinnitus (perception of sound in the ear when there is no external sound).
- Blurred eyesight.
- Feeling the heart pumping in the chest, flushing, increased sweating, night sweats
- Problems getting an erection, less sex drive.
- (Itchy) rash.
- Muscle pain, muscle tightness, muscle spasm.
- Increased yawning.
- Lack of appetite, weight loss.

### **Uncommon side effects (these can affect from 1 to 10 users in 1,000 patients treated)**

- Throat inflammation.
- Feeling disorientated, feeling sleepy, lack of motivation.
- Tasting things differently than usual, disturbance in attention, stiffness, spasms and involuntary movements of the muscles, muscle twitching, abnormal manner of walking.
- Poor sleep quality
- Burping, indigestion, gastroenteritis
- Vertigo, ear pain.
- Inflammation of the liver that may cause abdominal pain

- Large pupils (the dark centre of the eye), visual disturbance.
- Fast or irregular heart beat
- Sexual problems, including changes in ejaculation, orgasm.
- Abnormal periods, including heavy or prolonged periods.
- Allergic reactions, increased tendency to bruise, blisters or sensitivity to sunlight
- Increase in blood pressure, feeling cold in your fingers and/or toes, feeling dizzy ( particularly when standing up too quickly), cold sweats, shivering or fainting.
- An increased level of sugar in the blood.
- Need to pass more urine than normal, need to pass urine during the night, difficulty or inability to pass urine or having an urine flow decreased.
- Grinding of teeth, feeling hot/cold, thirst, throat tightness, nose bleeds.
- Weight gain.

**Rare side effects (these can affect from 1 to 10 users in 10,000 patients treated)**

- Decrease of activity of the thyroid gland.
- Dehydration.
- Mania (a disorder which symptoms are over activity, racing thoughts and decrease need for sleep).
- Bad breath.
- Increased pressure in the eye.
- Menopausal symptoms.
- Contraction of the jaw muscle.
- Increased level of cholesterol in the blood, low levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused), syndrome of inadequate secretion of anti-diuretic hormone (SIADH).

**Other possible side effects**

- Hallucinations, suicidal thoughts, behaviour aggression and anger.
- A sensation of restlessness or an inability to sit or stand still or “Serotonin syndrome” (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), fits.
- Passing bright red blood in your stools, vomiting blood, or black tarry stools (faeces).
- Having abnormal urine odour.
- Chest pain.
- Yellow colouration of the skin (jaundice), hepatic failure, Stevens-Johnson syndrome, sudden swelling of skin or mucosa (angioedema).

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## **5. HOW TO STORE ARICLAIM**

**Keep out of the reach and sight of children**

Do not use ARICLAIM after the expiry date which is stated on the carton.

Store in the original package. Do not store above 30°C.

## 6. FURTHER INFORMATION

### What ARICLAIM contains

The active substance is duloxetine.

Each capsule contains 30 or 60 mg of duloxetine (as hydrochloride).

The other ingredients are:

Capsule content: hypromellose, hydroxypropyl methylcellulose acetate succinate, sucrose, sugar spheres, talc, titanium dioxide (E171), triethyl citrate.

Capsule shell: gelatin, sodium lauryl sulphate, titanium dioxide (E171), indigo carmine (E132), iron oxide yellow (E172) (60 mg only) and edible green ink (30 mg) or edible white ink (60 mg).

Edible green ink: black iron oxide-synthetic (E172), yellow iron oxide- synthetic (E172), propylene glycol, shellac.

Edible White Ink: titanium dioxide (E171), propylene glycol, shellac, povidone.

### What ARICLAIM looks like and contents of the pack

ARICLAIM is a hard gastro-resistant capsule

Each capsule of ARICLAIM contains pellets of duloxetine hydrochloride with a covering to protect them from stomach acid.

ARICLAIM is available in two strengths: 30 and 60 mg.

The 30 mg capsules has an opaque white body, imprinted with '30 mg' and an opaque blue cap, imprinted with '9543'.

The 60 mg capsules has an opaque green body, imprinted with '60 mg' and an opaque blue cap, imprinted with '9542'.

ARICLAIM 30 mg is available in packs of 7, 28 and 98 capsules.

ARICLAIM 60 mg is available in packs of 28 and 98 capsules.

Not all pack sizes may be marketed.

### Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland BV, Grootslag 1-5,NL-3991 RA Houten, The Netherlands.

Manufacturer: Lilly S.A., Avda. De la Industria, 30,28108 Alcobendas, Madrid, Spain.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

#### **België/Belgique/Belgien**

S.C.S. Boehringer Ingelheim Comm.V.

Tél/Tel: +32 27 73 33 11

#### **България**

ТП "Ели Лили Недерланд" Б.В. - България

тел. + 359 2 491 41 40

#### **Česká republika**

Boehringer Ingelheim spol. s r.o.

Tel.: + 42 02 34 65 51 11

#### **Danmark**

Boehringer Ingelheim Danmark A/S

Tlf: +45 39 15 88 88

#### **Deutschland**

Boehringer Ingelheim Pharma GmbH & Co. KG

Tel: +49 (0) 69 50 50 83 09

#### **Luxembourg/Luxemburg**

S.C.S. Boehringer Ingelheim Comm.V.

Tél/Tel: +32 2 773 33 11

#### **Magyarország**

Boehringer Ingelheim Pharma

Tel.: +36 1 224 7120

#### **Malta**

Boehringer Ingelheim Ltd.

Tel: +356 25600 500

#### **Nederland**

Boehringer Ingelheim b.v.

Tel: +31 30 6 02 59 14

#### **Norge**

Boehringer Ingelheim Norway KS

Tlf: +47 66 76 13 00

**Eesti**

Boehringer Ingelheim Pharma GmbH

Tel: + 37 2 60 80 940

**Ελλάδα**

ΦΑΡΜΑΣΕΡΒ-ΛΙΑΛΥ Α.Ε.Β.Ε.

Τηλ: +30 210 629 4600

**España**

Dista S.A..

Tel: + 34 91 623 17 32

**France**

Boehringer Ingelheim France S.A.S.

Tél: +33 3 26 50 45 33

**Ireland**

Boehringer Ingelheim Ireland Ltd.

Tel: +353-(0) 1 661 4377

**Ísland**

Eli Lilly Danmark A/S, Útibú á Íslandi

Tel: + 354 520 34 00

**Italia**

Eli Lilly Italia S.p.A.

Tel: + 39- 055 42571

**Κύπρος**

Boehringer Ingelheim Ellas A.E.

Τηλ: +30 2 10 89 06 300

**Latvija**

Boehringer Ingelheim Pharma GmbH

Tel: +37 167 24 00 68

**Lietuva**

Boehringer Ingelheim Pharma Ges mbH

Tel.: +370 37 47 39 22

**This leaflet was last approved in**

**Österreich**

Boehringer Ingelheim Austria GmbH

Tel: +43 1 710 3739

**Polska**

Boehringer Ingelheim Sp.z o.o.

Tel.: +48 22 699 0 699

**Portugal**

Boehringer Ingelheim, Lda

Tel: +351 21 313 53 00

**România**

Eli Lilly România S.R.L.

Tel: + 40 21 4023000

**Slovenija**

Boehringer Ingelheim Pharma

Tel.: +386 1 586 40 00

**Slovenská republika**

Boehringer Ingelheim Pharma

Tel.: +421 2 5341 8445

**Suomi/Finland**

Oy Eli Lilly Finland Ab

Puh/Tel: +358 9 8545 250

**Sverige**

Boehringer Ingelheim AB

Tel: +46 8 721 21 00

**United Kingdom**

Boehringer Ingelheim Ltd.

Tel: +44 (0) 1256 315999

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.ema.europa.eu>.